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| 09/941,897 | 08/28/2001 | James Halbrook | 27866/37676 | 7824 |

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EXAMINER

KIFLE, BRUCK

ART UNIT

PAPER NUMBER

1624

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Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary

Application No.

09/941,897

Applicant(s)

Halbrook et al.

Examiner

Bruck Kifle, Ph.D.

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-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on Dec 9, 2002
- 2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 1-37 is/are pending in the application.
- 4a) Of the above, claim(s) 2-37 is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 1 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claims _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are a) ☐ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
- 11) ☐ The proposed drawing correction filed on _____ is: a) ☐ approved b) ☐ disapproved by the Examiner.
If approved, corrected drawings are required in reply to this Office action.
- 12) ☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

- 13) ☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
a) ☐ All b) ☐ Some* c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____.
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).
*See the attached detailed Office action for a list of the certified copies not received.
- 14) ☒ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).
a) ☐ The translation of the foreign language provisional application has been received.
- 15) ☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

- 1) ☒ Notice of References Cited (PTO-892) 4) ☐ Interview Summary (PTO-413) Paper No(s). _____
- 2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948) 5) ☐ Notice of Informal Patent Application (PTO-152)
- 3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s). 4 6) ☐ Other:

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Election/Restriction

Restriction to one of the following inventions is required under 35 U.S.C. 121:

- I. Claims 1-5 and 11, drawn to compounds of claim 1.
 - IA. Compounds wherein ring A is N-morpholinyl and each Z is CR³.
 - IB. Compounds wherein ring A is N-piperazinyl and each Z is CR³.
 - IC. Compounds wherein ring A is N-thiomorpholinyl and each Z is CR³.
 - ID. Compounds wherein ring A is N-piperidinyl and each Z is CR³.
 - IE. Compounds wherein ring A is pyranyl and each Z is CR³.
 - IF. Compounds not falling under subgroups IA-IE, but generically embraced by the claims. Should Applicants elect this group, election of specific values of ring A and Z is required.
- II. Claims 6-9 and 11, drawn to compounds of claim 6.
- III. Claim 10, drawn to individual compounds.
- IV. Claims 12-21, drawn to a the pharmaceutical composition of claim 12.
- V. Claim 22, drawn to a method of inhibiting DNA-PK activity.
- VI. Claims 23 and 24, drawn to a method of sensitizing a cell type to an agent that induces DNA lesions.
- VII. Claims 25 and 26, drawn to a method of potentiating a therapeutic regimen for treatment of a cancer.

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- VIII. Claim 27, drawn to a method of characterizing the potency of a test compound as inhibitor of a DNA-PK polypeptide.
- IX. Claims 28-31, drawn to a method of characterizing the potency of a test compound as an inhibitor of a DNA-PK polypeptide.
- X. Claims 32-37, drawn to an article of manufacture comprising an anti-cancer compound that induces double-strand DNA breakage in cells and a package insert.
- XI. Claim 35, drawn to an article of manufacture comprising a compound selected from a cytokine, a lymphokine, a growth factor and a hematopoietic factor and a package insert.
- XII. Claims 36 and 37, drawn to an article of manufacture comprising a pharmaceutical composition comprising a DNA-PK inhibitor of claim 1 or 6 in a pharmaceutically acceptable carrier and a package insert.

The inventions are distinct, each from the other because of the following reasons:

Compounds of the instant claims do not possess single structural element that is shared by all of the alternatives. There is no common structural feature shared by all of the alternatives.

The claims are drawn to structurally dissimilar compounds which are classified and searched separately which would be a serious burden to the office, require separate literature searches, raise different issues of patentability and are not art recognized equivalents. They are made and used independently.

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Compounds, corresponding compositions, a method of use and a process of making that are of the same scope are considered to form a single inventive concept.

The compounds of the instant claims are so diverse in scope that a prior art anticipating one compound under 35 USC 102 would not render obvious another compound of the same claim under 35 USC 103.

Should applicants traverse on the ground that the groups are not patentably distinct, applicant should submit evidence or identify such evidence now of record showing these groups to be obvious variants or clearly admit on the record that this is the case. In either instance, if the examiner finds one of the groups unpatentable over the prior art, the evidence or admission may and will be used in a rejection under 35 U.S.C. 103(a) of the other invention.

Applicant's election with traverse of the species of example 34 at pages 111 and 112 in Paper No. 7 is acknowledged. The elected compound falls under group IA above. The elected species is excluded by the proviso in claim 1 that reads "when A is morpholinyl, R² and R⁴ are hydrogen, and ZR³ is CH at each occurrence, then R¹ is different from -(CO)-CH₃". Nevertheless, the search has been conducted to embrace compounds wherein ring A is N-morpholinyl (optionally substituted by R⁴) and Z represents carbon at each occurrence (i.e., an optionally substituted phenyl).

Claims 2-37 are withdrawn from consideration because art was found (see MPEP 803.02.)

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Applicants are also advised of MPEP 803.02 Restriction - Markush Claims [R - 2], fourth paragraph, where is stated;

“As an example, in the case of an application with a Markush - type claim drawn to the compound C - R, wherein R is a radical selected from the group consisting of A, B, C, D, and E, the examiner may require a provisional election of a single species, CA, CB, CC, CD, or CE. The Markush - type claim would then be examined fully with respect to the elected species and any species considered to be clearly unpatentable over the elected species. If on examination the elected species is found to be anticipated or rendered obvious by prior art, the Markush - type claim and claims to the elected species shall be rejected, and claims to the non - elected species would be held withdrawn from further consideration. As in the prevailing practice, **a second action on the rejected claims would be made final.**” (emphasis added).

Claim Rejections - 35 USC § 112

Claim 1 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

i) The preamble of claim 1 reads “A DNA-PK inhibitor having a formula”. It is suggested to rewrite this as “A compound of formula” if the compound is being claimed. The way the claim is written is confusing as to what exactly is being claimed.

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- ii) In the definition of ring A, are additional substituents beyond the R^4 intended? If not deletion of the phrase “optionally substituted” is required because the structural formula depicts R^4 already.
- iii) In ring A, it is unclear whether the N is always the point of attachment to the aromatic ring. If so, this should be stated in the claim. If not, the N will have a dangling valency rendering the claim indefinite.
- iv) The term “substituted” without saying which substituents are intended is indefinite. One skilled in the art cannot say which substituents are permitted and which ones are not.
- v) The term “cycloalkyl” is indefinite because it is not known how many atoms make up the ring and what kind of a ring is intended (monocyclic, bicyclic, spiro, fused, bridged, saturated, etc.).
- vi) The term “heterocycloalkyl” is not normal nomenclature. Is it an -alkyl-heterocycle or just a heterocycle? The term is indefinite also because it is not known how many atoms make up the ring, which atoms are present and what kind of a ring (monocyclic, bicyclic, spiro, fused, bridged, saturated, etc.) is intended.
- vii) There is no difference between “carboxyl” and “carboxy” because the group $-COOH$ is understood. Deletion of one of them is required.
- viii) An aldehyde is not a radical but a class of compounds. Appropriate correction is required.
- ix) The sulfonyl radical is $-SO_2\cdot$. A dangling valency is present in this group.

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- x) The term “heteroaryl” is indefinite because it is not known how many atoms are present, how many and what kind of heteroatoms are involved, what size ring is intended and how many rings are present.
- xi) The term “acyl” is indefinite because one cannot say whether only alkanoyls are intended or whether acyls of acids of sulfur, phosphorous, arsenic, etc. are all intended.
- xii) A phosphate is not a radical but a compound. Appropriate correction is required.
- xiii) When R^1 and R^2 are taken together, the last phrase of the first paragraph on page 219, reads “said heteroatom optionally substituted with.....” Is a substituent on a heteroatom intended? It is unclear how. Also, it is unclear whether a monocyclic ring is intended or not. Is a saturated ring intended or unsaturated?
- xiv) In R^3 , the phrase “a halide derivative thereof” is unclear. A clarification is required because R^3 may be halo and it is unclear what else is intended.
- xv) In the proviso, the group ZR^3 is present which is in error. Correction is required.
- xvi) In the proviso, R^1 as $(C=CH_2)$ -phenyl is excluded. However, R^1 is not permitted to be $(C=CH_2)$ -phenyl (i.e. an alkenylene aryl group or a substituted alkenyl group) in the first place. A clarification is required

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless -

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(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claim 1 is rejected under 35 U.S.C. 102(b) as being anticipated by Wenk et al. (GB 2109373). The claim reads on the compound in page 32, line 34. The claim reads on this compound when ring A represents morpholinyl; Z is a carbon at each occurrence; R¹ is acyl (acetyl); R² is hydrogen and R³ represents halo (chloro) and hydroxy.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

Claim 1 is rejected under 35 U.S.C. 103(a) as being unpatentable over Eiden et al. (Archiv der Pharmazie (Weinheim, Germany) (1985), 318(4), 328-40). The reference teaches the compound of RN 97066-10-9 (see CAS abstract and structure of the compound). The claim differs by being a ring position isomer.

Position isomers are well established as being prima facie structurally obvious. See: Ex parte Engelhardt, 208 USPQ 343, 349; In re Mehta, 146 USPQ 284; In re Surrey, 138 USPQ 67; Ex parte Ulliyot 103 USPQ 185; Ex parte Naito 168 USPQ 437, 439; In re Norris 84 USPQ 459; Ex parte Allais 152 USPQ 66; Ex parte Henkel 130 USPQ 474; Ex parte Biel 124 USPQ

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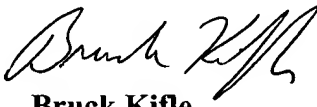
109; In re Crownse 150 USPQ 554; In re Fouche 169 USPQ 431; Ex parte Ruddy 121 USPQ 427; In re Wiechert 152 USPQ 249.

For example "Position Isomerism has been used as a tool to obtain new and useful drugs" (Engelhardt), and Position isomerism is a fact of close structural similarity" (Mehta, emphasis in the original).

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Bruck Kifle whose telephone number is (703) 305-4484.

The fax phone number for this Group is (703) 308-4556 or (703) 305-3592. Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Group receptionist whose telephone number is (703) 308-1235.

February 13, 2003


Bruck Kifle
Primary Examiner
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